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REVIEW

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Refractory septic shock: our updated pragmatic approach

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Abstract

Despite the refinement in guidelines and improving outcomes, a subset of patients with septic shock fails to respond to treatment and progresses into refractory septic shock with an associated high morbidity and mortality. This population remains underrepresented in clinical trials due to their heterogeneity, in addition to time and ethical constraints. As a large specialist referral centre, we propose an updated, pragmatic, and largely inexpensive approach based on our current clinical practice, which focuses on early multimodal therapy, aiming to reduce the detrimental effects associated with high-dose vasopressors.

Keywords Refractory septic shock, Multi-organ failure, Catecholamine toxicity, Toxic shock, Septic cardiomyopathy, Vasoplegic shock

Introduction

Since the previous version of this paper [1], there have been some significant advances in septic shock management. These improvements are largely attributable to the updated Surviving Sepsis Campaign (SSC) guidelines from 2021 [2] and refined patient selection in clinical trials. However, despite these innovations, a subgroup of patients continues to exhibit resistance to conventional consensus-based management and can be classified as having refractory septic shock.

Refractory septic shock remains an ill-defined syndrome with heterogeneous definitions but, in general, is characterised by hypotension with a requirement for high-dose vasopressor support in the presence of persistent tissue hypoperfusion and organ dysfunction despite adequate resuscitation [3]. There is increasing recognition of the need for early multimodal therapy for refractory shock to avoid unacceptable toxicity from catecholamine excess, such as tachyarrhythmias and limb or gastrointestinal ischaemia [4]. The traditional paradigm of stepwise addition of shock adjuncts, with escalating doses of catecholamines, may result in increased time to restoration of tissue and organ perfusion, past the point of reversibility [5], resulting in significant morbidity and mortality. Evolving evidence suggests improved outcomes with a more individualised approach and earlier initiation of multimodal, catecholamine-sparing therapy to avoid such toxicity and rapidly restore tissue perfusion [6, 7].

As a specialist Severe Respiratory and Cardiac Failure Centre in the UK, between our internal and referred cohorts, we advise on and treat over 50 patients every year with refractory septic shock where SSC recommendations and standard therapy have failed.

The aim of this paper is to describe a comprehensive set of treatment options for clinicians to restore organ perfusion and haemodynamic coherence and to minimise the detrimental effects of high-dose vasopressors and acid–base derangement.

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SHOUT
SHARE
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Initial approach

Buffered crystalloid and albumin

Assessment and optimisation of preload are the cornerstone of managing organ hypoperfusion in septic shock. Our practice is to use a combination of invasive cardiac output monitoring, serial echocardiography, and bedside dynamic clinical assessment to assess fluid responsiveness.

In agreement with the SSC guidelines [2], buffered isotonic crystalloid fluid remains the first choice for initial fluid resuscitation, followed by 20% human albumin solution if further volume replacement is required. Albumin has been associated with reduced mortality in patients with septic shock [8], more sustained haemodynamic effects [9], and potential improvement in the microcirculation [10].

Hydrocortisone and fludrocortisone

Although its survival benefit remains unclear, hydrocortisone has been shown to hasten shock resolution, and the recommendation to use it has been upgraded in the 2021 SSC guidelines [2]. Our practice is to administer hydrocortisone as a continuous infusion (200 mg daily) due to its potential benefits in promoting shock resolution [11]. There remains uncertainty over the role of fludrocortisone in improving shock outcomes with conflicting randomised controlled trials [12, 13]. However, subsequent meta-analysis [14] provide moderate evidence of a mortality benefit. Therefore, our approach is to add fludrocortisone 100 µg daily, until shock resolution, considering the potential for improved outcomes, lack of any safety concerns, low cost, and ease of enteral administration.

Vasopressin

Patients with refractory septic shock commonly exhibit catecholamine resistance with flattening of the noradrenaline dose–response curve. Vasopressin induces V1-receptor-mediated vasoconstriction and allows a reduction in noradrenaline requirement [15]. Vasopressin is considered once noradrenaline base is in the range of 0.2–0.3 mcg/kg/min. In line with the SSC guidelines and the results of the VANISH [16] and VASST [17] trials, we routinely limit vasopressin dose to a maximum of 0.04 IU/min to minimise the risk of ischaemia. Patients with acute or chronic pulmonary hypertension can further benefit due to a relative vasoactive-sparing effect on the pulmonary vasculature [18].

Femoral arterial access

Septic shock and high-dose vasopressors disrupt normal arterial pressure waveform propagation [19]. This can create a significant discrepancy, of up to 13 mmHg, between radial and femoral mean arterial pressures (MAP) [20], which can lead to unnecessary escalation of vasopressor dosing and toxicity. To mitigate this, we routinely use femoral arterial access for blood pressure monitoring as part of our vasopressor-sparing strategy.

Minimised and targeted sedation

Sedative medications may exacerbate hypotension through myocardial depression and systemic vasodilation [21]. We strictly titrate sedative agents to a target Richmond Agitation–Sedation Scale (RASS) of 0 to −2 or a bispectral index level of 40 to 60 if neuromuscular blockers are required, often allowing significant dose reduction. To reduce propofol requirements and its possible adverse haemodynamic impact, low-dose midazolam infusion may be added while in the rescue phase of shock resuscitation [21]. We acknowledge the prolonged half-life, potential for accumulation, increased risk of delirium, and potential for over-sedation with benzodiazepines, but short duration and daily spontaneous awakening trials limit these adverse effects.

Lower MAP targets

Blood pressure is used as a surrogate for perfusion, but this relationship is not linear and can be heavily disrupted in septic shock and during high endogenous and exogenous catecholamine states [22]. Observational studies in non-septic patients suggest that cerebral [23] and splanchnic [24] perfusion may remain acceptable at MAP values as low as 50–55 mmHg. Additionally, the 65 TRIAL [25] found that in critically ill patients, targeting MAP around 60 mmHg did not worsen outcomes.

While an initial MAP target of 65 mmHg seems a reasonable approach for many patients, the ideal MAP should be individualised [26] and may be lowered to 50–55 mmHg in selected younger patients without pre-existing hypertension or coronary artery disease. This approach requires close monitoring of tissue and organ perfusion, but it may avoid excessive peripheral vasoconstriction that can compromise the microcirculation and increase the risk of ischaemic complications.

Additional supportive measures and therapies

Inotropic support

Low cardiac output states due to septic cardiomyopathy are not uncommon in patients with refractory septic shock. These states can be identified using invasive cardiac output monitoring, serial echocardiography, and physiological surrogates, such as central venous saturation and venous-to-arterial CO_2 tension difference. Dobutamine has traditionally been used to increase cardiac contractility, but exacerbation of tachycardia and increased myocardial oxygen consumption may limit its usefulness in this context [27]. Though evidence is

limited [28, 29], milrinone is our preferred approach with typical doses of 0.1–0.3 µg/kg/min to mitigate concomitant vasodilatation, noting the prolonged half-life seen in acute kidney injury.

If macro-circulatory parameters fail to respond to first-line inodilators, or when stress-induced cardiomyopathy is suspected, we initiate levosimendan. This approach enhances myocardial contractility while minimising adrenergic stimulation and limiting myocardial oxygen consumption [30]. In the LeoPARDS study [31], levosimendan did not reduce organ dysfunction or 28-day mortality but was associated with increased rates of arrhythmia. However, patients were enrolled irrespective of cardiac index, and only a small proportion had cardiac dysfunction.

Enteral nutrition and replacement of thiamine

In patients with overt shock and mesenteric hypoperfusion, early enteral nutrition is either contraindicated or often limited to a 'trophic' feeding rate due to high gastric residual volumes. To avoid an increased risk of non-occlusive mesenteric ischaemia, we often rely on parenteral nutrition to reach adequate caloric targets, particularly in patients with multiple days of reduced intake, prior to transfer to our institution.

Thiamine (vitamin B1) supplementation may accelerate shock reversal in deficient patients [32]. Detection of thiamine deficiency using whole blood thiamine is expensive, time-consuming, and affected by the analytical method; additionally, thiamine reserve is easily depleted in critical illness [33] and by renal replacement therapy (RRT) [34]. Therefore, thanks to a safe pharmacological profile, a cost-effective way to optimise thiamine levels is to supplement systematically with intravenous multivitamin preparations. Our usual dosing is 500 mg of thiamine three times a day until shock has resolved.

Bicarbonate and renal replacement therapy

Severe acidosis leads to myocardial depression, vasodilatation, pulmonary vasoconstriction, and reduced sensitivity to catecholamines [35]. Sodium bicarbonate administration reduces the requirement for RRT [36] and possibly mortality in non-anion gap metabolic acidosis [37], but its role in the treatment of lactic acidosis is still a matter of contention.

Correction of macro-haemodynamic parameters and tissue hypoperfusion usually leads to resolution of lactic acidosis. However, in patients with refractory septic shock, vasodilatation and lactic acidosis may combine in a vicious cycle, where bicarbonate can be effective. Any beneficial effects of sodium bicarbonate can be dampened by side effects, such as increased carbon dioxide, with paradoxical acidosis, and hypocalcaemia, and particular attention should be given to prevent them [38].

Short-term high-dose RRT — up to 40–60 ml/kg/h — can be initiated early to rapidly improve metabolic status. Although large trials investigating prolonged high-dose RRT have been negative [39, 40], selected patients may benefit from short-term high-dose clearance as improved metabolic status can reduce vasopressor requirements and improve cardiac output [41]. Antimicrobial dosing and vitamin/trace element supplementation should be adjusted to offset excessive clearance.

Epoprostenol and glyceryl trinitrate

Persistent hypoperfusion despite adequate resuscitation often reflects uncoupling between macro- and microcirculation, driven by imbalances between regional vasoconstrictor and vasodilator signalling, both endogenous and exogenous [42]. Intravenous prostacyclins improve microcirculatory flow and are used in patients with Raynaud's disease [43] or frostbite [44]. Unfortunately, in septic shock, promising preliminary data [45] were not confirmed in subsequent large randomised controlled trials [46, 47]. However, enrolled patients only exhibit moderate signs of peripheral hypoperfusion.

In refractory septic shock with extensive peripheral mottling, we initiate a low-dose epoprostenol infusion (0.5–5 ng/kg/min) to improve microcirculatory flow [48] and reduce thrombotic risk and digital ischaemia. When titrated cautiously and kept within a low-dose range, any haemodynamic compromise can be mitigated, although we acknowledge that this approach should be investigated in further prospective trials. Prostacyclins are potent inhibitors of platelet aggregation, and we avoid their use in patients with severe thrombocytopenia or increased haemorrhagic risk. Where prostacyclins are contraindicated, glyceryl trinitrate infusion or local patches can be used [49].

Angiotensin II, methylene blue, and hydroxocobalamin

Patients with persistent hypotension and hypoperfusion despite preserved cardiac output and adequate preload optimisation may benefit from other vasopressor therapies that act via alternative pathways to re-establish perfusion pressure and so avoid excessive catecholamine exposure.

Relative deficiency of angiotensin II has been associated with worse outcomes in septic shock. The use of angiotensin II in septic shock increases blood pressure and decreases the need for standard vasopressors [50]. It has shown particular efficacy in patients on renin-angiotensin-aldosterone system (RAAS) inhibitors [51], although our experience remains limited.

The profound vasoplegia experienced with septic shock is contributed to by excessive production of nitric oxide (NO), which causes vasodilation through the activation of guanylate cyclase. Methylene blue (MB) specifically inhibits soluble guanylate cyclase within the NO pathway. Based on emerging literature in cardiac surgery [52] and in septic shock [53], MB may be used as a rescue therapy. MB also exhibits antioxidant properties [54] and may reduce sepsis-associated oxidative stress. We administer 1–2 mg/kg as a loading dose, followed by continuous infusion of 0.25–1 mg/kg/h, limiting the cumulative dose to 7 mg/kg, to reduce adverse effects [55]. Particular caution should be used in patients at risk of serotonin syndrome given the monoamine oxidase inhibiting property of MB [55].

High-dose hydroxocobalamin has also been used as an alternative rescue therapy [56]. It is an inhibitor of NO synthase, guanylate cyclase, and hydrogen sulphide, acting as a NO scavenging agent [57]. Our practice is to administer as a slow 5-g infusion over 3–4 h to prolong the NO scavenging effects, where NO production is likely ongoing, but further studies are required to demonstrate the efficacy, safety, and place in therapy of this novel agent. However, it is infrequently required if the above measures are applied and, in some countries, there are availability issues.

It should be noted that MB and hydroxocobalamin may induce colour changes in plasma that may affect pulse oximetry, blood leak detection in extracorporeal circuits, and interpretation of laboratory tests, such as anti-Xa monitoring [58].

Toxin-reducing antimicrobial therapy

Toxic shock syndrome frequently results in refractory septic shock through bacterial exotoxin release. Protein synthesis-inhibiting antimicrobials, such as clindamycin and linezolid, reduce toxin production *in vitro* [59], though observational studies report a variable impact on mortality [60, 61]. This variability is likely influenced

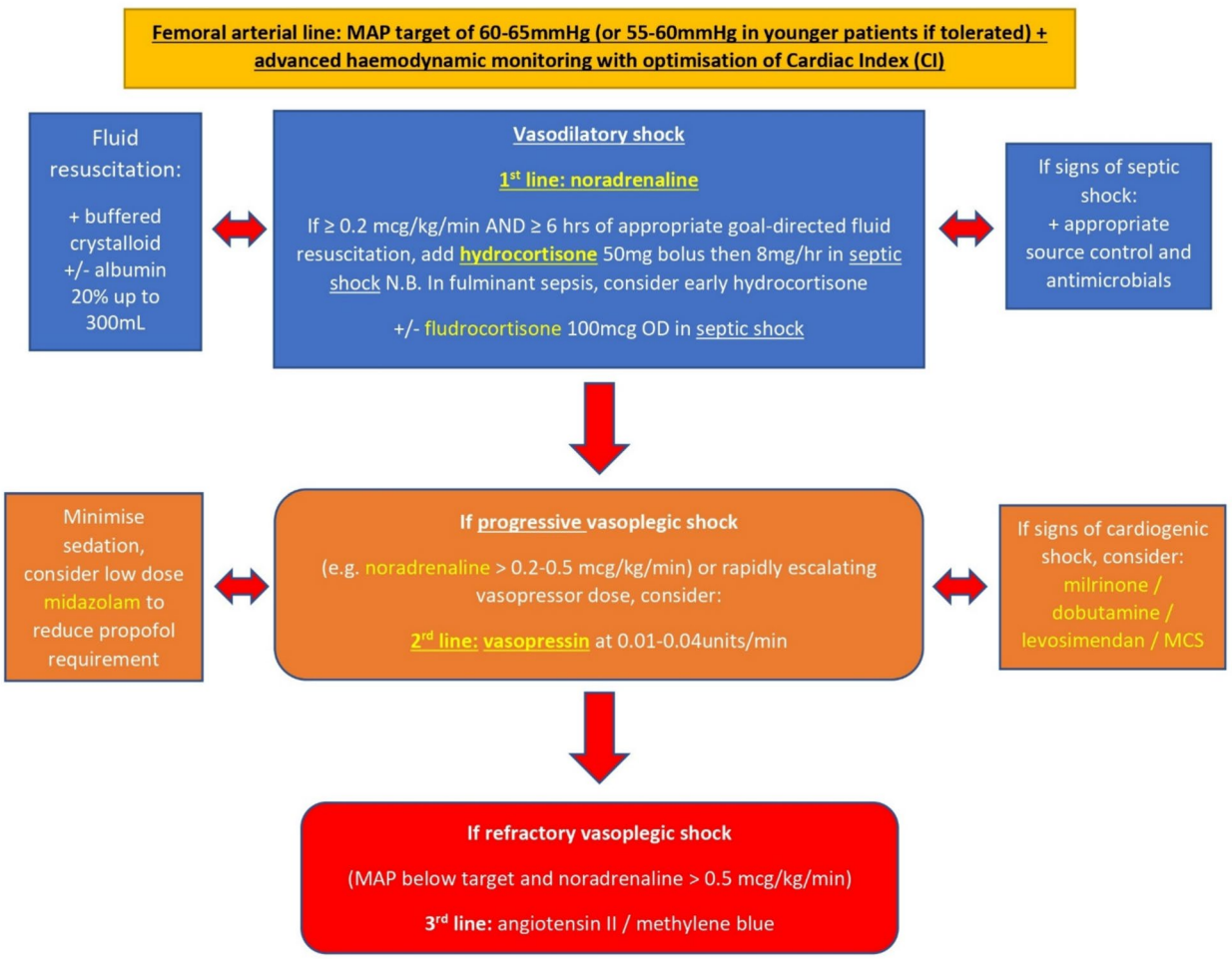
Femoral arterial line: MAP target of 60-65mmHg (or 55-60mmHg in younger patients if tolerated) + advanced haemodynamic monitoring with optimisation of Cardiac Index (CI)
Fluid resuscitation:
+ buffered crystalloid
+/- albumin 20% up to 300mL
Vasodilatory shock
1st line: noradrenaline
If ≥ 0.2 mcg/kg/min AND ≥ 6 hrs of appropriate goal-directed fluid resuscitation, add hydrocortisone 50mg bolus then 8mg/hr in septic shock N.B. In fulminant sepsis, consider early hydrocortisone
+/- fludrocortisone 100mcg OD in septic shock
If signs of septic shock:
+ appropriate source control and antimicrobials
Minimise sedation, consider low dose midazolam to reduce propofol requirement
If progressive vasoplegic shock
(e.g. noradrenaline > 0.2-0.5 mcg/kg/min) or rapidly escalating vasopressor dose, consider:
2rd line: vasopressin at 0.01-0.04units/min
If signs of cardiogenic shock, consider: milrinone / dobutamine / levosimendan / MCS
If refractory vasoplegic shock
(MAP below target and noradrenaline > 0.5 mcg/kg/min)
3rd line: angiotensin II / methylene blue

Fig. 1 Pharmacological management of vasodilatory shock — adapted from local guidance

by the timing of administration, with earlier treatment potentially being more effective [62]. In selected patients with rapid deterioration and signs suggestive of toxin-mediated illness, such as cutaneous or gastrointestinal involvement, we initiate protein synthesis-inhibiting antimicrobials prior to microbiological confirmation.

Intravenous immunoglobulin

The 2021 SSC guidelines [2] acknowledge the potential mortality benefit of intravenous immunoglobulin (IVIG), supported by multiple meta-analyses [63, 64], but recommend against the routine use of IVIG in septic shock given the cost, equity concerns, and feasibility in middle- and low-income settings. However, IVIG's anti-inflammatory and immunomodulation properties may benefit individual patients with a hyperinflammatory phenotype. As a result, we may consider IVIG (1–2 g/kg) in selected refractory septic shock patients where there is confirmed microbiology, clinical features, and/or a history highly suggestive of toxin-producing organisms [65].

Extracorporeal membrane oxygenation support

Extracorporeal membrane oxygenation (ECMO) can provide an effective temporising measure to achieve adequate oxygen delivery and acid–base correction in patients with refractory septic shock and septic cardiomyopathy with reduced ejection fraction [66]. ECMO eases the burden of conventional support by reducing mechanical ventilation power and vasoactive drug requirements. However, careful patient selection is absolutely essential (Figure 1).

Conclusion

Although many clinical trials in sepsis and septic shock have been negative, over the recent decades, mortality has declined [67], likely due to the gradual cumulative benefit of earlier initiation of multiple interventions and marginal gains. We propose a similar individualised and dynamic approach (Fig. 1) for patients with refractory septic shock, tailored to the patient's context. While the effect size of each individual intervention may be small, our local experience suggests that when applied in combination, this approach may be associated with improved shock outcomes [68].

This population remains underrepresented in clinical trials, and we recognise that some of our clinical approach is guided by expert opinion and local experience. Much uncertainty remains, but we hope to stimulate discussion and offer practical guidance, particularly since many of these strategies are low cost and broadly implementable.

Abbreviations

SSC	Surviving Sepsis Campaign
MAP	Mean arterial pressure
RASS	Richmond Agitation-Sedation Scale
BIS	Bispectral index
RRT	Renal replacement therapy
RAAS	Renin-angiotensin-aldosterone system
NO	Nitric oxide
MB	Methylene blue
IVIG	Intravenous immunoglobulin
ECMO	Extracorporeal membrane oxygenation
MCS	Mechanical circulatory support

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Authors' contributions

DW, CM and NI conceived the idea. FP and AWB drafted the initial manuscript. FH and SK formulated the figure. DW, CM, NI, MO, FH and SK edited the manuscript. All authors read and approved the final manuscript.

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Ethics approval and consent to participate

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Competing interests

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